transition state, TC1 ⇌ B13, are those centered at C-6 and C-7, while the highest transition state, TC2 ⇌ B10, presents large deviations at angles centered at C-7 and O-1. The relative energy among transition states is a consequence of the bond angle type suffering the largest deformation. Modification of an angle of C–C–C type requires less energy than that of one of C–C–O type, and both need less energy than deformation of one of C–O–C type due to both their natural bond angle and bending constants in the MM2 force field (109.5°, 107.4°, and 106.8°, and 0.45, 0.70, and 0.77 mdynes Å/rad, respectively).

Conclusions

The conformational dynamics of 1,4-dioxepane, **3**, has been fully studied by MM2 calculations. The compound shows twist-chair conformations (TC3, TC5, TC10, and TC12) in its ground state and pseudorotates within the C/TC family less freely than its parent hydrocarbon, cycloheptane **1**. The B/TB family of **3** presents two main peculiarities: (i) some B conformations are energy minima and two TB are energy maxima while B are maxima and TB minima in **1**, and (ii) only 12 stationary points (six maxima and six minima) compose its pseudorotational pathway. The interconversion between C/TC and B/TB families has also been studied and a barrier of 7.5 kcal/mol found.

Registry No. 1,4-Dioxepane, 505-68-0.

Supplementary Material Available: Tables containing the internal dihedral angles and relative energies for the stationary points of the conformational pathways of **3** and table containing the intraannular bond angles for the energetically unique transition states between C/TC and B/TB families as well as their deviation from the MM2 natural values (4 pages). Ordering information is given on any current masthead page.

A Short Synthesis of (±)-Gephyrotoxin 223AB

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Bicyclic Gephyrotoxin 223AB (**1**), an alkaloid found in the skins of brightly colored Central and South American frogs of the genus *Dendrobates*,[1-3] has attracted wide interest in the last few years because of its promising pharmacological activity. These indolizidine and related compounds "probably represent a structural class of noncompetitive blockers of neuromuscular transmission".[4] This interest has resulted in a few syntheses of **1**,[5] also in its enantiomeric natural (−) form,[6] and in the syntheses of stereoisomers of **1**.[7]

We report now a new short and efficient synthesis of (±)-GTX 223AB (**1**), based upon a 1,3-dipolar cycloaddition of a cyclic nitrone with complete stereochemical control. Our synthesis is characterized by a very short number of steps and by the fact that only one separation of isomers is required and can be executed before the final step on stable materials that are easier to handle.

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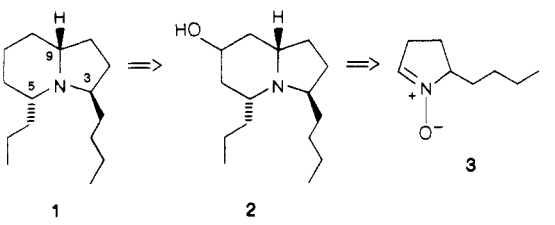
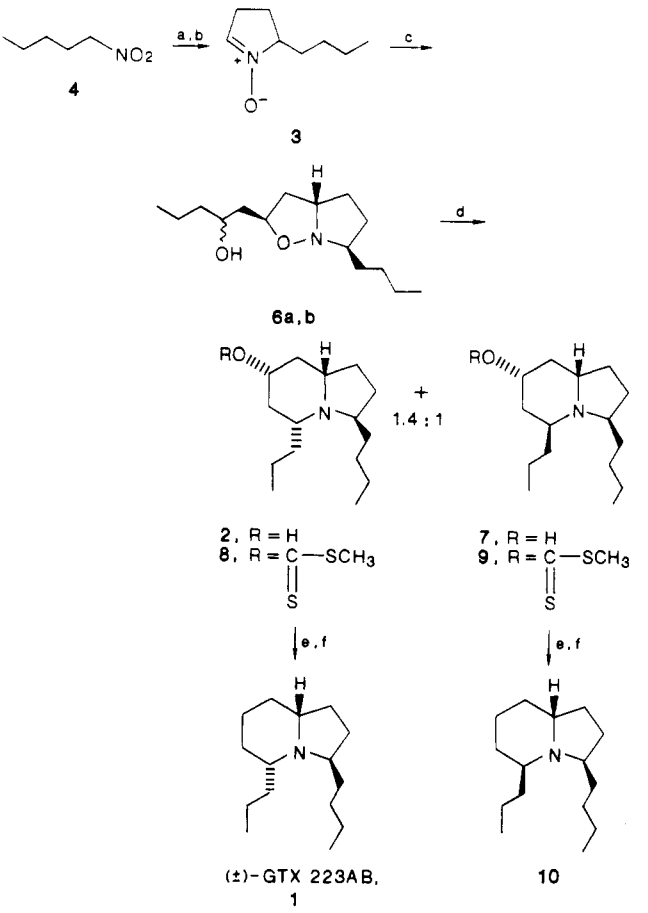
Scheme I



Scheme II[a]



[a] (a) NaOMe/MeOH, H_2C=CHCHO, 0 °C, 57%; (b) 4-nitrooctane aldehyde (**5**), Zn/AcOH, 5 °C, 51%; (c) 4-hydroxyheptene, 110 °C, 46 h, 61%; (d) (i) MsCl, Py; (ii) H_2/Pd/C 10%, 57 h, 67%; (e) NaH, CS_2, MeI, 67 °C, 84%; (f) Bu_3SnH, AIBN, 110 °C.

We focused on the alcohol **2** as a suitable intermediate, containing the right relative 5*E*,9*E* stereochemistry, from which the GTX 223AB can be obtained by known reactions, without affecting the chiral centers. Compound **2** is easily accessible from a functionalized isoxazolidine[8]

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prepared in turn by 1,3-dipolar cycloaddition of the nitrone **3** (Scheme I).

Results and Discussion

The nitrone **3** was synthesized by Michael addition of nitropentane **4** and acrolein, followed by reduction of the resulting aldehyde **5** and cyclization according to a recent modification of an old procedure[9] (Scheme II). The cycloaddition of **3** with 1-hepten-4-ol in refluxing toluene afforded a mixture of only two diastereoisomers **6a** and **6b** in almost 1:1 ratio and 61% yield. ^1H and ^{13}C NMR spectra allow the assignment of the two isoxazolidines as diastereoisomeric at the alcoholic group, having the 2-hydroxypentyl chain on the convex face of the molecule. The signal at δ 3.00 for the proton at the carbon bearing the *n*-butyl chain in **6** is in agreement with a hydrogen in a trans relationship with the nitrogen doublet and significantly differs from the value of δ 3.75 for the bridgehead proton, cis to the nitrogen doublet.[10] The relative *E* stereochemistry of these two protons, as confirmed by NMR data, derives from an energetically favored anti transition state in the cycloaddition process. This preferential anti approach in the cycloaddition of substituted cyclic nitrones has already been observed by us[11] and Tufariello.[12] The relative stereochemistry of the two centers is, therefore, already settled at this stage, as required for the target **1**.

Treatment of the alcohols **6a,b** with methanesulfonyl chloride in pyridine at −10 °C afforded the corresponding mesylated intermediates: we were unable to assign these intermediates as the mesylated alcohols[8] or the mesylate salts produced by spontaneous cyclization at the isoxazolidine nitrogen.[13] The intermediates, however, without purification, were hydrogenated over Pd/C at atmospheric pressure to afford a 1.4:1 mixture of the two isomeric alcohols **2** and **7** in 67% overall yield. The two alcohols can be separated by flash chromatography and carefully analyzed by spectroscopic means. The major compound is identified as the indolizidinol **2** with 5*E*,9*E* stereochemistry and the minor one as its epimer at C-5. IR spectrum of **2** showed diagnostic Bohlmann's bands[14] at 2801 and 2680 cm^{-1}, absent in the spectrum of **7**. The two compounds, moreover, are characterized by two sets of proton signals relative to C-3, C-5, and C-9 that are diagnostic for the structural assignment. The isomer **2** has values of δ 3.55, 3.27, and 2.51 for the three protons of which two are more shielded if compared with values of δ 3.82, 3.25, and 2.98 in the minor isomer **7**. This shielding pattern has already been connected by Sonnet[15] with the number of axial protons in related structures. The mass spectra of the two isomers, moreover, are closely related to the mass spectra of the relative indolizidines.[2] The alcohol **2** shows the same fragmentation picture as GTX 223AB (**1**),[18] and the alcohol **7** the same as (5*Z*,9*E*)-3-*n*-butyl-5-*n*-propylindolizidine[2] (**10**) (see the Experimental Section).

The deoxygenation of the alcohol **2** was achieved, by using the Barton procedure,[16] by reaction of the xanthate with tributyltin hydride. For convenience, the separation of the two diastereoisomeric indolizidinols was made at the level of the xanthates. Reaction of pure **8** with tributyltin hydride and catalytic azoisobutyronitrile in refluxing toluene afforded, after column chromatography with ethyl acetate–10% triethylamine,[17] pure **1** in 79% yield. The compound, as predicted, was found to have identical spectra with those of natural GTX 223AB.[18] Similarly, the epimer **10** was prepared from the xanthate **9**.

Experimental Section

All reactions were carried out under nitrogen. Kugelrohr distillations were carried out by the Büchi GKR-50 distillator; the oven temperature is reported. NMR spectra ($CDCl_3$ as solvent) were recorded on Varian XL 300 (^1H, 300 MHz) and Varian FT-80A (^{13}C, 20 MHz) spectrometers and are reported in ppm from tetramethylsilane; notations s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectra were recorded at 70 eV by GC inlet on a 5790A-5970A Hewlett-Packard instrument. IR spectra were recorded on Perkin-Elmer 283 and 881 spectrophotometers, and combustion analysis were carried out with a Perkin-Elmer 240 C elemental analyzer.

3,4-Dihydro-2-*n*-butyl-2*H*-pyrrole 1-Oxide (3). Activated Zn (3 g, 46 mmol) was added in one portion to an ice-cooled solution of 4-nitrooctanaldehyde **5** (4 g, 23 mmol; obtained in 57% yield by Michael addition[8] of nitropentane **4** to acrolein) in 70 mL of EtOH, followed by glacial acetic acid (5.3 g, 92 mmol) drop by drop. The addition required 1 h, and during this time the temperature was kept below 5 °C. Stirring was maintained for another 2 h, and the flask was then set in a refrigerator for 2 days. The precipitate was then filtered and thoroughly washed with EtOH. The alcoholic solution was concentrated, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed twice with saturated Na_2CO_3 solution. The organic solution was dried (Na_2SO_4) and concentrated to give an oil, which afforded, after Kugelrohr distillation (130 °C, 0.07 mmHg), 1.65 g (51%) of the nitrone **3**. The compound appeared to be 98% pure by GC analysis: MS *m/z* (relative intensity) 141 ($3^{\bullet+}$, 9), 124 (39), 85 (74), 84 (44), 68 (55), 55 (37), 41 (100); ^1H NMR δ 6.87 (m, 1 H), 3.95 (m, 1 H), 2.65 (m, 2 H), 2.38 (m, 1 H), 2.16 (m, 1 H), 1.94 (m, 1 H), 1.59 (m, 1 H), 1.2–1.5 (m, 4 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 133.37 (d), 71.37 (d), 30.81 (t), 26.10 (t), 25.60 (t), 23.91 (t), 21.61 (t), 12.98 (q); IR (liquid film) 2940, 2850, 1575, 1450, 1335, 1230, 1190 cm^{-1}.

Hexahydro-6-*n*-butyl-2-(2-hydroxypentyl)pyrrolo[1,2-*b*]isoxazoles (6a,b). A mixture of the nitrone **3** (1.29 g, 9.2 mmol) with 1-hepten-4-ol (2.09 g, 18.4 mmol) in 50 mL of toluene was heated at reflux 46 h. After removal of volatiles, purification of the residue by chromatography through a short pad of silica gel (El, $CHCl_3$) gave an oil consisting of an unseparable 1:1 mixture of the isoxazolidines **6a** and **6b** (1.43 g, 61%). Kugelrohr distillation (150 °C, 0.07 mmHg) afforded a sample for combustion analysis. (Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.54; H, 11.45; N, 5.48. Found: C, 70.66; H, 11.32; N, 5.70): MS *m/z* (relative intensity) 255 ($6^{\bullet+}$, 2), 212 (13), 198 (53), 180 (10), 168 (9), 142 (27), 126 (75), 112 (100), 85 (12), 68 (30), 55 (30), 41 (43); ^1H NMR δ 4.30 (isomer **6a**, m, 1 H), 4.18 (isomer **6b**, m, 1 H), 3.87–3.68 (m, 2 H), 3.0 (m, 1 H), 2.2–1.1 (m, 19 H), 0.89 (t, J = 7 Hz, 3 H), 0.87 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 72.99 (d), 68.10 (d), 67.05 (d), 63.41 (d) (isomer **6a**); 74.69 (d), 70.51 (d), 67.13 (d), 63.86 (d) (isomer **6b**); 42.41 (t), 41.38 (t), 40.35 (t), 40.23 (t), 39.71 (t), 39.48 (t), 34.43 (t) (2 C), 30.74 (t), 30.62 (t), 29.62 (t) (2 C), 28.85 (t) (2 C), 22.60 (t)

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(18) Spectra of natural GTX 223AB: ref 4, MS *m/z* (relative intensity) 223 (1), 222 (2), 180 (85), 166 (100); ref 3, ^{13}C NMR δ 59.0 (d), 58.5 (d), 56.6 (d), 35.9 (t), 32.4 (t), 30.9 (t), 30.0 (t), 29.1 (t), 26.3 (t), 24.9 (t), 24.6 (t), 22.9 (t), 18.9 (t), 14.5 (q), 14.1 (q).

(2 C), 18.61 (t), 18.47 (t), 13.79 (q) (4 C); IR (liquid film) 3400, 2970, 2940, 2880, 1470, 1460, 1380, 1130, 1075, 1030 cm^{-1}.

(5*E*,9*E*)- and (5*Z*,9*E*)-Octahydro-3-*n*-butyl-5-*n*-propylindolizin-7-ol (2 and 7). Freshly distilled $MeSO_2Cl$ (0.45 mL, 669 mg, 5.8 mmol) was added dropwise to a solution of the alcohols **6a,b** (746 mg, 2.9 mmol) in 7.5 mL of anhydrous pyridine, cooled to −10 °C. After 4 h of being stirred at the same temperature, the reaction mixture was poured in ice and extracted with CH_2Cl_2 (four times, 15 mL). The combined organic layers were washed with 1 N aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to yield the methanesulfonate derivatives quantitatively. The crude oil was dissolved in MeOH (10 mL), added with 26 mg of 10% Pd on C, and hydrogenated under atmospheric pressure of hydrogen. After 57 h the reaction, monitored by TLC, was completed. After filtration on Celite, the methanolic solution was treated with 1 N aqueous NaOH (3 mL), and the mixture was stirred for 2 h. The solution was then concentrated, and the yellow residue was dissolved in CH_2Cl_2 (20 mL) and washed twice with H_2O. The organic layer was dried (Na_2SO_4) and concentrated, and the oil obtained was chromatographed on a short pad of silica gel by eluting in sequence with CH_2Cl_2, EtOAc, and MeOH. The more polar fractions contained a 1.4:1 mixture of the indolizidinols **2** and **7** (471 mg, 67%). The two isomers can be separated by flash chromatography (El, ethyl acetate): **7**, R_f = 0.35; **2**, R_f = 0.25. Anal. Calcd for $C_{15}H_{29}NO$: C, 75.26; H, 12.21; N, 5.85. Found: C, 75.10; H, 12.08; N, 6.11.

2 (5*E*,9*E*): MS *m/z* (relative intensity) 239 ($2^{\bullet+}$, 1), 238 (1), 196 (91, loss propyl), 182 (100, loss butyl), 152 (17), 41 (9); ^1H NMR δ 3.61 (br s, 1 H), 3.55 (m, 1 H), 3.27 (m, 1 H), 2.51 (m, 1 H), 2.12–1.81 (m, 3 H), 1.65–1.05 (m, 16 H), 0.88 (t, J = 7.2 Hz, 3 H), 0.86 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 69.20 (d), 57.80 (d), 57.44 (d), 53.77 (d), 40.85 (t), 39.64 (t), 35.17 (t), 28.99 (t), 28.76 (t), 26.77 (t), 25.43 (t), 22.71 (t), 18.65 (t), 13.80 (q), 13.74 (q); IR (CCl_4) 3621, 3364 (broad), 2959, 2931, 2873, 2860, 2801 and 2680 (Bohlmann's bands), 1464, 1380, 1184, 1117, 1094, 1012 cm^{-1}.

7 (5*Z*,9*E*): MS *m/z* (relative intensity) 239 ($7^{\bullet+}$, 2.7), 238 (2.1), 196 (100, loss propyl), 182 (98, loss butyl), 152 (23), 41 (16); ^1H NMR δ 3.82 (m, 1 H), 3.25 (m, 1 H), 2.98 (m, 1 H), 2.80 (m, 1 H), 2.08–1.85 (m, 2 H), 1.65–1.0 (m, 17 H), 0.87 (m, 6 H); ^{13}C NMR δ 65.22 (d), 58.75 (d), 54.96 (d), 53.34 (d), 36.60 (t), 35.56 (t), 35.17 (t), 31.95 (t), 28.99 (t), 28.33 (t), 28.17 (t), 22.87 (t), 20.25 (t), 14.01 (q), 13.90 (q); IR (CCl_4) 3617, 3345 (broad), 2959, 2931, 2872, 2860, 1467, 1378, 1144, 1192, 1101, 1019 cm^{-1}.

(5*E*,9*E*)- and (5*Z*,9*E*)-Octahydro-3-*n*-butyl-5-*n*-propylindolizin-7-ol *S*-Methyl Dithiocarbonate (8 and 9). A mixture of 120 mg (5.0 mmol) of sodium hydride, 756 mg (3.16 mmol) of the alcohols **2** and **7**, 21 mg (0.316 mmol) of imidazole, and 20 mL of dry tetrahydrofuran was heated to reflux for 3 h, followed by the addition of 1 mL (17.0 mmol) of carbon disulfide. The mixture was warmed under reflux for 30 min, and 1 mL (17.0 mmol) of methyl iodide was added. The mixture was warmed for 30 min longer and then partitioned between 50 mL of CH_2Cl_2 and 50 mL of water. The aqueous phase was extracted twice with 20 mL of CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The oil residue was flash chromatographed (El, EtOAc 15% in petroleum ether) to give two fractions: R_f = 0.6, 409 mg (mixture of isomers **9** and **8** in 9:1 ratio, yield 39%), and R_f = 0.4, 468 mg (pure **8**, yield 45%). **8** (Anal. Calcd for $C_{17}H_{31}NOS_2$: C, 61.95; H, 9.48; N, 4.25. Found: C, 61.82; H, 9.69; N, 3.96): MS *m/z* (relative intensity) 329 ($8^{\bullet+}$, 0.9), 286 (37), 272 (100), 222 (48), 178 (88), 164 (16), 126 (14), 122 (11), 55 (16), 41 (13); ^1H NMR δ 5.48 (tt, J = 11.4, 4.5 Hz, 1 H), 3.24 (br t, J = 9 Hz, 1 H), 2.59 (m, 1 H), 2.51 (s, 3 H), 2.27 (m, 2H), 1.92 (m, 2H), 1.69–0.95 (m, 15 H), 0.91 (t, J = 6.9 Hz, 3 H), 0.89 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 214.96, 81.59, 57.52, 56.49, 53.13, 36.80, 35.44, 35.33, 29.22, 28.84, 26.82, 25.22, 22.72, 18.56, 18.46, 14.22, 13.96; IR (CCl_4) 2960, 2930, 2880, 2860, 2810, 1220, 1050 cm^{-1}. **9**: ^1H NMR δ 5.78 (tt, J = 9.0, 3.4 Hz, 1 H), 3.37 (m, 1 H), 3.05 (m, 1 H), 2.87 (m, 1 H), 2.53 (s, 3 H), 2.09–1.88 (m, 2 H), 1.88–1.03 (m, 16 H), 0.92 (m, 6 H); ^{13}C NMR δ 214.78, 80.00, 57.93, 54.12, 53.12, 35.85, 35.56, 32.52, 29.09, 28.14, 27.54, 22.93, 20.25, 20.19, 18.62, 18.56, 13.90 (2 C).

(5*E*,9*E*)-Octahydro-3-*n*-butyl-5-*n*-propylindolizine (1). A solution of the xanthate **8** (110 mg, 0.33 mmol) in dry toluene (5 mL) was added dropwise to a boiling mixture of tributyltin hydride (0.135 mL, 146 mg, 0.50 mmol) and azoisobutyronitrile (catalytic) in the same solvent (5 mL). The resulting solution was warmed under reflux for additional 5 h and then concentrated in vacuo. The residue was chromatographed over silica gel, eluting first with petroleum ether and then with 15% ethyl acetate in petroleum ether. Eventually **1** was eluted from the column with 9:1 ethyl acetate–triethylamine: 59 mg (79%); volatile pale yellow oil; MS *m/z* (relative intensity) 223 ($1^{\bullet+}$, 1), 222 (2), 181 (11), 180 (88), 167 (12), 166 (100), 164 (2), 124 (13), 122 (9), 81 (6), 55 (11), 41 (20); ^1H NMR δ 3.29 (m, 1 H), 2.38 (m, 2 H), 1.95–0.97 (m, 20), 0.91 (t, J = 7 Hz, 3 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 58.90 (d), 58.39 (d), 56.50 (d), 35.77 (t), 32.26 (t), 30.84 (t), 29.94 (t), 29.01 (t), 26.25 (t), 24.86 (t), 24.56 (t), 22.83 (t), 18.85 (t), 14.39 (q), 14.03 (q); IR ($CDCl_3$) 2970, 2940, 2880, 2860, 2810 cm^{-1}.

(5*Z*,9*E*)-Octahydro-3-*n*-butyl-5-*n*-propylindolizine (10). The above procedure was repeated on the epimer **9**; with eluent ethyl acetate, **10** was isolated as a volatile pale yellow oil, yield 38%: MS *m/z* (relative intensity) 223 ($10^{\bullet+}$, 2), 222 (3), 181 (13), 180 (100), 166 (95), 124 (13), 55 (9), 41 (15); ^1H NMR δ 3.07 (m, 1 H), 2.55 (m, 1 H), 2.44 (m, 1 H), 1.87–1.04 (m, 20 H), 0.90 (m, 6 H); ^{13}C NMR δ 58.42 (d), 56.09 (d), 52.38 (d), 32.28 (t), 29.29 (t), 28.63 (t), 28.54 (t), 28.16 (t), 27.62 (t), 22.95 (t), 22.80 (t), 20.67 (t), 19.20 (t), 14.35 (q), 13.96 (q).

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Registry No. (±)-**1**, 81076-50-8; (±)-**2**, 118798-53-1; (±)-**3**, 118798-54-2; **4**, 628-05-7; (±)-**5**, 118798-55-3; (±)-**6** (isomer 1), 118798-56-4; (±)-**6** (isomer 2), 118916-45-3; (±)-**7**, 118916-43-1; (±)-**8**, 118798-57-5; (±)-**9**, 118916-44-2; (±)-**10**, 81076-53-1; CH_2=CHCHO, 107-02-8; (±)-1-hepten-4-ol, 111321-98-3.

Synthesis of *O*-Phosphotyrosine-Containing Peptides. 1. Synthesis of *P*Tyr-Leu-Gly via Benzyl Phosphate Protection

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The recent recognition of tyrosine phosphorylation as an important step in several cellular processes[1-7] has necessitated the need for the development of a synthetic methodology suitable for the production of synthetic *P*Tyr peptides for use as model substrates. In contrast to the well-documented synthetic methodology outlined for the preparation of *P*Ser peptides,[8-11] the synthetic methodology for the preparation of *P*Tyr peptides is not as well developed and is limited to only two recent significant studies. In the first of these studies, Valerio et al.[12] prepared Leu-Arg-Arg-Ala-*P*Tyr-Leu-Gly in an overall yield

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